REMARKS

Claims 1, 3, 19, 31, 32, 36 and 37 have been amended to include the article "the" as suggested by the Examiner. Claims 5 and 34 have been amended to clarify the intended invention. Claims 1, 31 and 36 have been amended to specify that what is being claimed is a method to identify female individuals at risk for developing preeclampsia associated with the magnesium binding defect. Support for this amendment can be found in the instant specification, for example at [0024]. It is believed that none of these amendments constitute new matter and their entry is requested.

Rejection of Claims 1, 3-6 and 19 under 35 U.S.C. § 112, first paragraph

The Examiner has maintained the rejection of claims 1, 3-6 and 19 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. In particular, it was asserted that the specification is deficient in teaching how to use the invention because Applicant has not shown a direct link between the detection of the peptides of SEQ ID NOs: 1, 2, and 4 and the detection of preeclampsia. (Official Action page 4) Applicant respectfully traverses this rejection. As discussed below in detail, in view of the knowledge in the prior art, the specification provides evidence demonstrating that levels of amidated peptides of SEQ ID NOs: 1, 2, and 4 (the "Peptides") are lower in the rat model of magnesium binding defect as compared to the level of Peptedes in controls. Evidence that lower than normal levels of the Peptides are correlated with the magnesium binding defect is provided throughout the instant specification, for example at paragraphs [0018], [0034], [0042-0047], [0056] and Examples 2, 3, and 7.

The instant specification reports Applicant's discovery that the Peptides are components in normal plasma that promote magnesium binding to plasma membranes, and as such can correct the magnesium binding defect. See paragraph [0047]. The discoveries reported provide

evidence of the correlation between the levels of Peptides and the magnesium binding defect, i.e., increasing levels of the Peptides decreases the presence or extent of the magnesium binding defect through the process of promoting binding of Mg^{2+} to the cell membrane. The discovery of this correlation makes possible a method to aid in identifying a female individual at risk for developing preeclampsia associated with the magnesium binding defect. See paragraphs [0024] and [0054]. The Examiner acknowledges that the specification teaches: 1) that the administration of Peptides to rats *in vivo* corrected hypertension and the magnesium binding defect; and 2) that *in vitro* incubation of Peptides with human erythrocytes increased magnesium binding to the plasma membrane. *See*, Official Action page 4. However, the Examiner required clarification of support for Applicant's additional statement in the Response at page 10 that: "the levels of Peptides in rat models in which the magnesium binding defect was observed are lower than normal levels of Peptides found in [control] rat models without the magnesium binding defect." Applicant appreciates the Examiner's identification of the outstanding issue, and offers the following clarification of this statement.

The knowledge in the art at the time Applicant made the discoveries reported in the present specification includes the following:

1) There is an association of subnormal binding of magnesium to plasma membranes of somatic cells with an individuals' susceptibility to develop disorders such as essential hypertension and insulin resistance. The binding of magnesium by erythrocyte membranes is returned to normal by incubating erythrocytes from essential hypertensive patients with blood plasma from normotensive subjects. *See,* Mattingly et al., (1991)) *Clin Exper Hyper-Theory and Practice* A13:65-82. (paragraph [0013])

2) There is decreased binding of magnesium ion (Mg^{2+}) by erythrocyte membranes from essential hypertensive patients. *Id.* (paragraph [0042])

3) There exists a significant inverse correlation between concentration of magnesium tightly bound to plasma membranes and average blood pressure, i.e., reduced concentration of Mg^{2+} tightly bound to plasma membranes correlates with higher than normal blood pressure. *Id.* (paragraph [0042])

4) Magnesium ion concentration in erythrocyte ghosts and arterial tissue of the spontaneously hypertensive rat model (SHR) is significantly less than in these tissues from male normotensive controls (Wistar-Kyoto; WKY) of the same age. *See,* Wells and Agrawal (1992)) *Can. J. Physiol & Pharmacol* 70:1225:1229. (paragraph [0043])

5) The magnesium ion concentration in erythrocyte ghosts from SHR is increased to the control (normal) value, and not above, by incubating SHR erythrocytes with normal (WKY) blood plasma. As such, it is demonstrated that some component present in normal plasma promotes binding of magnesium to plasma membranes. However, SHR plasma did not affect the Mg^{2+} concentration in normal (control; WKY) erythrocyte ghosts. (*Id.*) (paragraph [0013]) In summary, the prior art had established that there is some component of normal plasma that promotes the binding of magnesium to plasma membranes, and that these promoters are missing, or present at a lower concentration, in the plasma of hypertensive rat model SHR.

This describes the state of the art at the time the Applicant discovered that: the Peptides, components of normal blood plasma, promote binding of magnesium to the plasma membrane, and as such can correct or ameliorate the magnesium binding defect; and coined the term magnesium binding defect ("MgBD") to describe the previously recognized subnormal binding of magnesium to plasma membranes of somatic cells of individual having disorders such as

essential hypertension, type 2 diabetes, and preeclampsia. It therefore logically follows from Applicant's discovery of the Peptides as promoters of magnesium binding, that the Peptides are at a lower concentration in the SHR rat model, in which the magnesium binding defect exists, as compared to the levels of Peptides in the normal controls.

This reasoning is further supported by Applicant's discovery that the Peptides correct, or ameliorate the magnesium binding defect in those disorders associated with the defect. As a result, one of skill in the art would recognize that Peptide level correlates with the risk of developing preeclampsia. Stated differently, Applicant has demonstrated that the levels of the Peptides in plasma from rat models in which the magnesium binding defect was observed are lower than normal levels of the Peptides found in rat models without the magnesium binding defect. Further evidence substantiating this correlation is provided through examples demonstrating: 1) the *in vivo* effectiveness of the intravenous administration of the Peptides in increasing magnesium binding (and in reducing blood pressure) (Example 2; paragraph [0047]); 2) demonstration that binding of magnesium to erythrocyte membranes from essential hypertensive patients was returned to normal by *in vitro* incubation with the Peptides (Example 3), and 3) demonstration that the Peptides promote magnesium binding in magnesium deficient erythrocytes while incubation of deficient erythrocytes with magnesium in absence of Peptides had no effect on magnesium binding (Example 7).

To summarize, the instant specification provides evidence that a significantly lower than normal level of Peptides correlates with the presence of magnesium binding defect, and, together with the teachings of the specification that preeclampsia is associated with the magnesium binding defect, the specification enables one skilled in the relevant art to make and use the claimed invention. While Applicant does not wish to be limited to a particular mode of action or

explanation of how the invention works, Examiner's attention is respectfully directed to the accompanying Declaration under Rule 1.132 (Declaration A) of Ibert C. Wells, the inventor of the present application.

The Examiner has also noted that Applicant's previous amendment of claim 1 and presentation of claims 31 and 36 apparently removed the indication that the claimed method be performed on female patients. Applicant has amended the claims herein to clarify that the method is to be performed on female individuals.

The Examiner repeats his position that "predisposition indicates that something (in this case, preeclampsia) is more likely than not to happen at a future date." Applicant respectively disagrees. "More likely than not" means more than 50% of the time. Detection of a predisposition to a condition does not mean that the condition will necessary occur in greater than 50% of individuals that test positive. In other words, the position predictive value (probably that a patient who tests positive has the disease) may be less than 50%. While Applicant disagrees with the Examiner's interpretation of the meaning of "predisposition", in the interest of early allowance, Applicant has amended the claims to recite a method to identify females at risk for developing preeclampsia. This amendment is supported in the specification, for example at paragraph [0024].

The Official Action cites Page et al. as further basis for this rejection. Specifically, the Examiner asserts that Page et al. makes the finding of a decreased level of Peptide as indicative of preeclampsia unclear, and that Page et al. supports a conclusion that the correlation between level of Peptide and preeclampsia is unpredictable. Applicant strongly disagrees. Several points are made here in response to this basis for rejection. First, the Examiner acknowledges that Page et al. is silent as to the levels of Peptides. (Official Action page 5) The claimed invention

involves the measurement of levels of Peptides, not levels of NKB (or other tachykinins). There is no limitation in the claims requiring that the method measure the levels of tachykinins or tachykinin peptides. It is urged that the Official Action has referred to a limitation which is not present in the claims.

Second, a specification that discloses information on how to make and use the invention must be accepted unless the Patent Official provides sufficient reason to doubt the accuracy of the disclosure. Ex parte Bhide, 42 USPQ2d 1441, 1147 (Bd. Pat. App. & Int'f 1996) ("A specification which contains a statement of the manner and process of using the invention in terms which correspond in scope to those used in defining the subject sought to be patented must be taken as in compliance with the 'how to use' requirement of the first paragraph of 35 USC Section 112 unless there is reason to doubt the objective truth of the statement. In re Brana 34 USPQ 1436 (Fed. Cir. 1995); In re Marzocchi, 169 USPQ 367 (CCPA 1971).") For the reasons discussed herein, Page et al. simply does not provide sufficient reason to doubt the accuracy of the disclosure of the present specification.

Third, the Examiner acknowledges that since Page et al. is silent as to the levels of Peptides, it is possible that detection of lower levels of the Peptides is correlated with preeclampsia. (Official Action page 5) As set forth in detail above, the specification provides the required evidence demonstrating that Peptide levels actually correlate with the presence of the magnesium binding defect, and further that preeclampsia is associated with the magnesium binding defect. As such, the specification demonstrates that detection of lower than normal levels of Peptide has predictive power concerning female individuals at risk for developing preeclampsia.

In summary, in as much as Page et al. reports only findings of NKB levels in pregnant women with preeclampsia, does not disclose or suggest the levels of Peptides, and further,

because the instant specification provides adequate disclosure for one in the art to make and use the claimed invention, Page et al. does not make the correlation between the levels of Peptides and preeclampsia "unpredictable".

The Official Action also cites the Merck Manual of Diagnosis and Therapy, 17th edition (1999) ("Merck") for reporting that the etiology of preeclampsia was unknown. Applicant does not understand this basis for rejection. It appears that Merck may have been cited as representative of the state of the art of the invention. However, that the Merck reference did not report detection of Peptides as predictive of preeclampsia, at the time the instant application was filed, in no way makes the discoveries reported in the specification, or the novel method of the present claims, unpredictable. Applicant urges that the state of the art of concern, that of peptide detection in body fluid, is sufficiently predictable that one of ordinary skill in the relevant art could use the specification as a guide to practice the invention.

In summary, Applicant urges that the correlation between levels of the Peptides and the risk of an individual developing preeclampsia is not unpredictable, and that a skilled artisan could, in view of the teachings of the present specification, use and carry out the claimed method without undue experimentation.

In view of the teachings in the specification of the correlation of lower levels of Peptides, and the association of the magnesium binding defect with the risk of developing preeclampsia, and in further view of the comments set forth above, it is urged that the claims are fully enabled and it is requested that the rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

Rejection of Claims 19 and 31-35 Under 35 U.S.C. §112, first paragraph

The Examiner has rejected Claim 19 and new Claims 31-35 under 35 U.S.C. 112, first paragraph, on the basis that the specification, while being enabling for a method of measuring

peptides consisting of SEQ ID NO:1 and SEQ ID NO:4 is not enabling for methods of measuring peptides consisting of SEQ ID NO:2. Applicant submits that the specification would enable one of ordinary skill in the art to practice the full breadth of the claimed invention and respectfully traverses the Examiner's rejection.

In the Official Action mailed April 8, 2005, the Examiner cited Couraud et al. in support of this assertion, specifically, that "antibodies with the requisite binding specificity are not readily generated" (Office Action, page 8). Applicant emphasizes that the practice of independent claims 19 and 31 is not limited to the use of monoclonal antibodies, nor is the practice of the other independent claims (and many of their dependents) so limited. However, recognizing that Claims 32-35 are limited to immunological procedures, Applicant provides the following in response.

Couraud et al. disclose a single procedure for preparing the immunogen used to generate antibodies to Substance P (SP). Specifically, Couraud et al. disclose use of bovine serum albumin (BSA) as a carrier and 1, 5-dinitrofluoro-2,4-dinitrobenzene (DFDB) as a coupling agent. The Examiner's attention is respectfully directed to the accompanying Declaration under Rule 1.132 (Declaration B) of Ibert C. Wells, the inventor of the present application. It is clear from this Declaration B that, as a result of the coupling method reported by Couraud et al., the attachment site of SP to the carrier is via the carboxyl group on SP and therefore does not allow for the presentation of an amidated carboxyl group to the immune system. Furthermore, it clarifies that Couraud et al. evaluate the cross-reactivity of their five selected monoclonal anti-SP antibodies and polyclonal serum using SP fragments that do not include an amidated carboxyl group (See page 1712).

Claims 19 and 31-36 are directed to a method for identifying females at risk for developing preeclampsia comprising measuring the levels of the peptide of SEQ ID NO:2 which is the amidated amino acid sequence Phe-Gly-Leu-Met-NH_2. One method of practicing the present invention employs immunological procedures. For example, the instant specification teaches that antigenic substances may vary in their abilities to generate an immune response, and that the host immune system may be boosted by coupling a weak immunogen, such as a peptide, to a carrier. [0029] It further teaches exemplary carriers and means for conjugating a peptide to a carrier [0029]. The Examiner acknowledged that these methods were routine and known in the art (4/8/05 Office Action, page 5). Therefore, Applicant urges that, based on the teachings of the disclosure that the amidated tetrapeptide of SEQ ID NO:2 corrects the magnesium binding defect in erythrocyte membranes ([0022]), one skilled in the art on the filing date of the present application would know how to select a conjugation protocol that links the carrier molecule to the N-terminus of SEQ ID NO:2. Such a methodology would present the amidated C-terminal carboxyl group to the immune system, and thereby enable the skilled artisan to make and use the claimed antibodies.

The Examiner based his rejection regarding antibodies to SEQ ID NO:2 solely on the Couraud et al. reference and the lack of cross-reactivity of Couraud et al.'s polyclonal serum and anti-SP monoclonal antibodies to an amino acid sequence, Phe-Gly-Leu-Met. The Examiner states that Couraud et al. "indicates that antibodies with requisite binding specificity are not readily generated" (Office Action, page 5, emphasis added). However, the fact that some amount of work must be performed to reach a successful end does not mean that a claimed composition is not enabled.

> "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. 'The key word is 'undue,' not 'experimentation.'
>
> The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. ... The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 8 U.S.P.Q.2d 1400, 1404.

As noted in Wands, the need for routine experimentation and screening is allowable and does not mean that an invention is not enabled. Examiner admits that the coupling strategies set forth in the present application involve routine procedures, known in the art. The fact that in order to practice the invention one skilled in the art would need to select from known carrier proteins and conjugating methodologies, and that antibody positive hybridomas would need to be screened for antibodies with the desired reactivity, does not mean that the claimed antibodies are not enabled.

Furthermore, objective enablement, not actual reduction to practice, is all that is required, as stated by the court in *Fiers v. Revel*, 984 F.2d 1164 (Fed. Cir. 1993):

> [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. (emphasis in original) 984 F.2d at 1171-1172.

In view of the foregoing, it is urged that the instant specification enables the full breadth of the claims and requests that this rejection under 35 U.S.C. 112, first paragraph, be withdrawn.

Rejection of Claims 5 and 34 Under 35 U.S.C. §112, second paragraph

The Examiner has rejected Claims 5 and 34 under 35 U.S.C. §112, second paragraph, as indefinite. Applicant has amended Claims 5 and 34 to clarify the peptides to which cross reactivity is claimed. Therefore, withdrawal of this rejection is respectfully requested.

In view of the foregoing amendments and remarks, it submitted that the claims remaining for active consideration in this application are in condition for allowance. Accordingly, favorable action at an early date will be appreciated. If the examiner is of the view that any issue remains unresolved, it is respectfully suggested that Applicant's undersigned attorney may be contacted by telephone at the number set forth below.

Respectfully submitted,

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